REMARKS

The claims have been amended in accordance with the helpful suggestions presented at the interview. In claim 66, functional language has been added with respect to both item (d) and new item (e) which is derived from former claim 63. The functional language constitutes that discussed and agreed upon. New dependent claims 70-74 merely recite elements (a)-(e) of claim 66 individually. All other claims have been canceled.

The Objection and the Rejections Under 35 U.S.C. § 112, Second Paragraph

It is believed that the amendments to the claims dispose of the objection and rejections under the second paragraph of § 112. Only claim 66 and claims dependent thereon (70-74) remain in the case. Clearly claims 70-74 are properly dependent on claim 66 as they simply recite the alternative elements of claim 66 individually. Reference to Figure 2 has been deleted as has "stringent conditions," "conservative substitution" and "a peptide region of at least 5 amino acids."

Accordingly, the rejections under 35 U.S.C. § 112, paragraph 2, may be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 56-58, 66 and 67 were rejected as lacking enablement in part due to putatively inadequate averments concerning the deposited subject matter. It is believed that the substance of this rejection is now applicable only to claim 66, part (c) and to new claim 72.

Applicants hereby state that the deposit of ATCC Accession No. PTA-1894 was made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

OK

It is believed that the foregoing disposes of the aspect of this rejection relating to the deposit.

In another portion of this rejection, claims 57-62, 64 and 66-69 were rejected as failing to show that applicants had possession of a genus of proteins which includes proteins other than those of SEQ. ID. No.: 2, *i.e.*, an asserted lack of adequate written description. This basis for rejection is thus applicable only to claim 66, parts (d) and (e), and to new claims 73 and 74. It is respectfully submitted that new claims 70-72 and the remaining paragraphs of claim 66 are free of this rejection.

However, reconsideration of this rejection is respectfully requested. As discussed and agreed upon at the recent Examiner Interview, only a very limited genus of proteins is claimed and the required functional nature of the protein (a 55P4H4-related protein that binds to an antibody that specifically binds the protein of SEQ. ID. No.: 2) and the required structural metes and bounds (at least 90% homologous) define a reasonable genus, as does the combination of this same functional language with the requirement for a fragment containing at least 30 amino acids. As noted in Example 14 of the Guidelines on Written Description, a 95% homology range is exemplified as considered within reason; it is believed 90% homology is of sufficiently similar scope. A fragment containing 30 amino acids is sufficient to characterize the protein in terms of its immunospecificity. Further, the Office offers no reasons to doubt that the genera claimed would not have at least one comparable utility to SEQ. ID. No.: 2 or that they would be even difficult, much less require further invention, to synthesize the members of these genera. Clearly, applicants are in possession of these genera as obtaining such peptides and proteins would be routine, and the Office has provided no rationale to doubt the operability of the claimed genera. *In re Marzocchi*, 439 F2d 220, 169 USPQ 367 (CCPA 1971).

In another portion of this rejection, claims 56-69 were rejected as non-enabled because the subject matter is said not to be useful.

First, it is understood that a single utility is sufficient to support a claim to a composition. One such utility, described in the specification, is the use of the protein to raise antibodies which can then be employed, *e.g.*, to diagnose the presence of the protein in tumors. Applicants submit that this utility is substantial, specific and credible and is well supported by the specification.

As a preliminary matter, applicants wish to address the argument made by the Office that positive mRNA results are not indicative of protein expression. Enclosed herewith is the Declaration of Dr. Pia Challita-Eid demonstrating that this is simply not the case. While the Office cites a number of documents which show that production of protein may be regulated at the translational level, and that the levels of protein produced may not correspond to the levels of mRNA detected, there is no teaching in any of the cited documents that under normal circumstances, there is no protein produced even when mRNA is present. On the contrary, a strong qualitative correlation is shown between the presence of protein encoded by mRNA and the presence of mRNA itself. The only document cited that appears to relate a single instance where, under some conditions, no protein is found when mRNA is present (Alberts) cannot be said to typify the situation ordinarily encountered. As attested by Dr. Eid's declaration, the absence of protein even in the presence of mRNA is an exception to a widely established and well recognized rule. Furthermore, in many cases, a reported lack of protein expression is due to technical limitations of the protein detection assay. For instance, the available antibody may only detect denatured protein but not native protein present in a cell. In other instances, the half-life of the protein is very short; thereby the steady-state protein levels are merely below the detectable range in that assay.

With this in mind, applicants call the attention of the Office to the expression data provided by Northern blots set forth in the specification. Dr. Eid's declaration establishes that these data are relevant to showing that the claimed protein is present in malignant, but not the corresponding normal tissue. It will also be noted that even if the protein is present in some normal tissues, this does not negate the utility of the protein as a diagnostic for cancer progression in tissues where it is not expressed normally. A diagnostic utility is predicted, in one embodiment, by testing tissues where there is no normal expression; in this context, testing the tissues where normal expression is found is simply irrelevant.

The pertinent data are found in Figures 6C, 7, 8, 9 and 16-17. As shown in Figure 6C, the gene encoding the claimed 55P4H4 protein is highly expressed in the prostate cancer cell line in lane 2, but not in normal prostate (lane 1). This alone shows the value of antibodies raised against the protein as a diagnostic. In the event it is thought that the absence of expression in some cancer cell lines somehow undermines the utility, applicants point out that this is not the case. It is typical that not all cancers associated with the same organ will express the same abnormal protein. All this means is that the absence of the protein does not show that the tissue is normal, but the presence of the protein demonstrates that the tissue is not normal.

Figure 7 shows the expression of the 55P4H4 gene in xenographs formed from the cell line that highly expressed the gene in Figure 6C. This demonstrates that expression occurs not only in the cell lines themselves, but also when the tumor is present *in vivo*.

Figure 8 shows the expression of this gene in a number of cancer cell lines thus demonstrating that it is present in types of cancer not limited to prostate. Figure 9 shows the expression of the gene in actual patient samples. There can be no question that expression of this gene acts as a marker for cancer in this context. Figures 16 and 17 confirm these results.

Thus, as demonstrated in the specification, the proteins claimed are useful at least for raising antibodies useful in assays to detect the presence of cancer in a variety of tissues. While applicants do not agree with the analysis made by the Office that alternative utilities, such as use in anticancer vaccines, use to screen for cancer drugs, and the like, are not credible, it is superfluous to address these contentions as the specification adequately supports the utility focused on above.

With respect to the objection that the teachings of the specification cannot be extrapolated to clinical use, applicants point out that this is not required. The Federal Circuit articulated this in *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995), holding that all that is required is a showing that the method in which the materials are useful is sufficiently promising to be worthy of further development. If that were not the case, as the Court, observed biologicals and drugs would never be developed. To obtain the data the Office presently appears to demand requires a substantial commitment of resources. The commitment will not be made if exclusivity cannot be provided in advance. In fact, U.S. laws, from the Constitutional era forward, are in place to assure that the progress of science and useful arts are promoted by securing such exclusive patent rights.

For these reasons, the rejection based on lack of utility may properly be withdrawn.

The Rejections Under 35 U.S.C. § 102

Only claims 68 and 69 were rejected as anticipated. These claims have been canceled, thus obviating this basis for rejection.

CONCLUSION

The claims have been amended to obviate the rejections for lack of clarity and improper dependence. The rejections with regard to scope are inapplicable to claims 70-72 and it is

believed that claims 73 and 74 and the claim from which they depend, claim 66, describe limited genera of the scope acknowledged by the Office in its Guidelines to be proper.

The rejection of the claims on the basis of an asserted lack of utility is believed in error as applicants have shown that their data provide sufficient guidance and credibility to meet the legal standard for utility, in addition applicants meet this standard as set forth in *In re Brana*, *supra*. Thus, applicants believe that claims 66 and 70-74 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 511582001200.

Respectfully submitted,

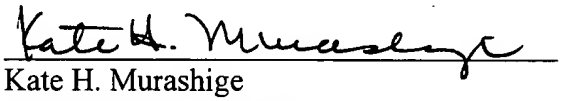
Dated: March 14, 2003 By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the paragraphs on page 4, line 35 to page 5, line 18, as follows:

Figure 11. Hydrophilicity amino acid profile of 55P5H4 determined by computer algorithm sequence analysis using the method of Hopp and Woods (Hopp T.P., Woods K.R., 1981. Proc. Natl. Acad. Sci. U.S.A. 78:3824-3828) accessed on the Protscale website at the world wide web address [(http://www.]expasy.ch/cgi-bin/protscale.pl[)] through the ExPasy molecular biology server.

Figure 12. Hydropathicity amino acid profile of 55P5H4 determined by computer algorithm sequence analysis using the method of Kyte and Doolittle (Kyte J., Doolittle R.F., 1982. J. Mol. Biol. 157:105-132) accessed on the ProtScale website at the world wide web address [(http://www.]expasy.ch/cgi-bin/protscale.pl[)] through the ExPasy molecular biology server.

Figure 13. Percent accessible residues amino acid profile of 55P5H4 determined by computer algorithm sequence analysis using the method of Janin (Janin J., 1979 Nature 277:491-492) accessed on the ProtScale website at the world wide web address [(http://www.]expasy.ch/cgi-bin/protscale.pl[)] through the ExPasy molecular biology server.

Figure 14. Average flexibility amino acid profile of 55P5H4 determined by computer algorithm sequence analysis using the method of Bhaskaran and Ponnuswamy (Bhaskaran R., and Ponnuswamy P.K., 1988. Int. J. Pept. Protein Res. 32:242-255) accessed on the ProtScale website at the world wide web address [(http://www.]expasy.ch/cgi-bin/protscale.pl[)] through the ExPasy molecular biology server.

Figure 15. Beta-turn amino acid profile of 55P5H4 determined by computer algorithm sequence analysis using the method of Deleage and Roux (Deleage, G., Roux B. 1987 Protein Engineering 1:289-294) accessed on the ProtScale website at the world wide web address [(http://www.]expasy.ch/cgi-bin/protscale.pl[)] through the ExPasy molecular biology server.

Please amend the paragraph on page 21, lines 3-10, as follows:

As discussed herein, redundancy in the genetic code permits variation in 55P4H4 gene sequences. In particular, it is known in the art that specific host species often have specific codon preferences, and thus one can adapt the disclosed sequence as preferred for a desired host. For example, preferred analog codon sequences typically have rare codons (i.e., codons having a usage frequency of less than about 20% in known sequences of the desired host) replaced with higher frequency codons. Codon preferences for a specific species are calculated, for example, by utilizing codon usage tables available on the INTERNET such as: at the world wide web address [http://www.]dna.affrc.go.jp/~nakamura/codon.html.

Please amend the paragraphs on page 24, lines 11-24, as follows:

Additional illustrative embodiments of the invention disclosed herein include 55P4H4 polypeptides comprising the amino acid residues of one or more of the biological motifs contained within the 55P4H4 polypeptide sequence set forth in Figure 2 or Figure 3. Various motifs are known in the art, and a protein can be evaluated for the presence of such motifs by a number of publicly available sites (see, e.g.: the world wide web addresses [http://]pfam.wustl.edu/; [http://]searchlauncher.bcm.tmc.edu/seq-search/struc-predict.html; [http://]psort.ims.u-tokyo.ac.jp/; [http://www.]cbs.dtu.dk/; [http://www.]ebi.ac.uk/interpro/scan.html; [http://www.]expasy.ch/tools/scnpsit1.html; Epimatrix™ and Epimer™, Brown University, [http://www.]brown.edu/Research/TB-HIV_Lab/epimatrix/epimatrix.html; and BIMAS, [http://]bimas.dcrt.nih.gov/[.]).

Motif bearing subsequences of the 55P4H4 protein are set forth and identified in Table XIX.

Table XX sets forth several frequently occurring motifs based on pfam searches at the world wide web address [(http://]pfam.wustl.edu/[)]. The columns of Table XX list (1) motif name abbreviation, (2) percent identity found amongst the different member of the motif family, (3) motif name or description and (4) most common function; location information is included if the motif is relevant for location.

Please amend the paragraph on page 25, lines 2-11, as follows:

In another embodiment, proteins of the invention comprise one or more of the immunoreactive epitopes identified in accordance with art-accepted methods, such as the peptides set forth in Tables V-XVIII. CTL epitopes can be determined using specific algorithms to identify peptides within an 55P4H4 protein that are capable of optimally binding to specified HLA alleles (e.g., Table IV (A) and Table IV (B); Epimatrix™ and Epimer™, Brown University, at the world wide web address [http://www.]brown.edu/Research/TB-HIV_Lab/epimatrix/epimatrix.html; and BIMAS, at the world wide web address [http://]bimas.dcrt.nih.gov/). Moreover, processes for identifying peptides that have sufficient binding affinity for HLA molecules and which are correlated with being immunogenic epitopes, are well known in the art, and are carried out without undue experimentation. In addition, processes for identifying peptides that are immunogenic epitopes, are well known in the art, and are carried out without undue experimentation either *in vitro* or *in vivo*.

Please amend the paragraph on page 26, line 19-page 27, line 5, as follows:

CTL epitopes can be determined using specific algorithms to identify peptides within an 55P4H4 protein that are capable of optimally binding to specified HLA alleles (e.g., Table IV (A) and Table IV (B); Epimatrix™ and Epimer™, Brown University at the world wide web addresses [(http://www.]brown.edu/Research/TB-HIV_Lab/epimatrix/epimatrix.html); and BIMAS, [http://]bimas.dcrt.nih.gov/). Illustrating this, peptide epitopes from 55P4H4 that are presented in the context of human MHC class I molecules HLA-A1, A2, A3, A11, A24, B7 and B35 were predicted (Tables V-XVIII). Specifically, the complete amino acid sequence of the 55P4H4 protein was entered into the HLA Peptide Motif Search algorithm found in the Bioinformatics and Molecular Analysis Section (BIMAS) web site listed above. The HLA peptide motif search algorithm was developed by Dr. Ken Parker based on binding of specific peptide sequences in the groove of HLA Class I molecules and specifically HLA-A2 (see, e.g., Falk et al., Nature 351: 290-6 (1991); Hunt et al., Science 255:1261-3 (1992); Parker et al., J. Immunol. 149:3580-7 (1992); Parker et al., J. Immunol. 152:163-75 (1994)). This algorithm allows location and ranking of 8-mer, 9-mer, and 10-mer peptides from a complete protein sequence for predicted binding to HLA-A2 as well as numerous other HLA Class I molecules.

Many HLA class I binding peptides are 8-, 9-, 10 or 11-mers. For example, for class I HLA-A2, the epitopes preferably contain a leucine (L) or methionine (M) at position 2 and a valine (V) or leucine (L) at the C-terminus (see, e.g., Parker et al., J. Immunol. 149:3580-7 (1992)). Selected results of 55P4H4 predicted binding peptides are shown in Tables V-XVIII herein. In Tables V-XVIII, the top 50 ranking candidates, 9-mers and 10-mers, for each family member are shown along with their location, the amino acid sequence of each specific peptide, and an estimated binding score. The binding score corresponds to the estimated half-time of dissociation of complexes containing the peptide at 37°C at pH 6.5. Peptides with the highest binding score are predicted to be the most tightly bound to HLA Class I on the cell surface for the greatest period of time and thus represent the best immunogenic targets for T-cell recognition.

Please amend the paragraph on page 45, line 32-page 46, line 5, as follows:

Genetic immunization methods can be employed to generate prophylactic or therapeutic humoral and cellular immune responses directed against cancer cells expressing 55P4H4. Constructs comprising DNA encoding a 55P4H4-related protein/immunogen and appropriate regulatory sequences can be injected directly into muscle or skin of an individual, such that the cells of the muscle or skin take-up the construct and express the encoded 55P4H4 protein/immunogen. Alternatively, a vaccine comprises a 55P4H4-related protein. Expression of the 55P4H4-related protein immunogen results in the generation of prophylactic or therapeutic humoral and cellular immunity against cells that bear 55P4H4 protein. Various prophylactic and therapeutic genetic immunization techniques known in the art can be used (for review, see information and references published at [Internet] the world wide web address [www.]genweb.com).

Please amend the paragraph on page 46, lines 17-34, as follows:

CTL epitopes can be determined using specific algorithms to identify peptides within 55P4H4 protein that are capable of optimally binding to specified HLA alleles (e.g., Table IV (A) and Table IV (B); Epimer™ and Epimatrix™, Brown University at the world wide web addresses [(http://www.]brown.edu/Research/TB-HIV_Lab/epimatrix/epimatrix.html[)];

and, BIMAS, [(http://]bimas.dcrt.nih.gov/). In a preferred embodiment, the 55P4H4 immunogen contains one or more amino acid sequences identified using one of the pertinent analytical techniques well known in the art, such as the sequences shown in Tables V-XVIII or a peptide of 8, 9, 10 or 11 amino acids specified by an HLA Class I motif (e.g., Table IV (A)) and/or a peptide of at least 9 amino acids that comprises an HLA Class II motif (e.g., Table IV (B)). As is appreciated in the art, the HLA Class I binding groove is essentially closed ended so that peptides of only a particular size range can fit into the groove and be bound, generally HLA Class I epitopes are 8, 9, 10, or 11 amino acids long. In contrast, the HLA Class II binding groove is essentially open ended; therefore a peptide of about 9 or more amino acids can be bound by an HLA Class II molecule. Due to the binding groove differences between HLA Class I and II, HLA Class I motifs are length specific, i.e., position two of a Class I motif is the second amino acid in an amino to carboxyl direction of the peptide. The amino acid positions in a Class II motif are relative only to each other, not the overall peptide, i.e., additional amino acids can be attached to the amino and/or carboxyl termini of a motif-bearing sequence. HLA Class II epitopes are often 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acids long, or longer than 25 amino acids.

Please amend the paragraph on page 56, lines 18-23, as follows:

Sequence analysis of 55P4H4 reveals homology to a protein that is regulated by hypoxia (PCT/US98/17296, WO 99/09049). The 55P4H4 ORF is 32% identical and 55% homologous to RTP779 over a 180 amino acid region, and 32% identical and 54% homologous to RTP801, the rat orthologue of RTP779 (Fig. 4). 55P4H4 is predicted to be a cytoplasmic protein by PSORT analysis at the world wide web address [(http:/]psort.ims-u-tokyo.ac.jp/form.html[)] with a lower possibility of nuclear or mitochondrial localization.

Please amend the paragraph on page 58, lines 23-28, as follows:

This vector and the mapping program at the world wide web address [http://www-]genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl placed 55P4H4 to chromosome 4q22.3-24. A variety of chromosomal abnormalities in 4q22.3-24 including amplifications have been identified as frequent cytogenetic abnormalities in a number of different cancers. Nilbert et al., 1988,

Cancer Genet. Cytogenet. 34(2): 209-218; Yeatman et al., 1996, Clin. Exp. Metastasis 14(3):246-252; and Joos et al., 2000, Cancer Res. 60(3): 549-552.

Please amend the paragraph on page 59, lines 25-27, as follows:

Figures 11, 12, 13, 14, and 15 depict graphically five amino acid profiles of the 55P5H4 amino acid sequence, each assessment available by accessing the ProtScale website at the world wide web address [(http://www.]expasy.ch/cgi-bin/protscale.pl[)] on the ExPasy molecular biology server.

Please amend the paragraph on page 73, lines 20-27, as follows:

Antibody efficacy on tumor growth and metastasis formation is studied, e.g., in a mouse orthotopic prostate cancer xenograft model. The antibodies can be unconjugated, as discussed in this Example, or can be conjugated to a therapeutic modality, as appreciated in the art. We demonstrate that anti-55P4H4 mAbs inhibit formation of both the androgen-dependent LAPC-9 and androgen-independent PC3-55P4H4 tumor xenografts. Anti-55P4H4 mAbs also retard the growth of established orthotopic tumors and prolonged survival of tumor-bearing mice. These results indicate the utility of anti-55P4H4 mAbs in the treatment of local and advanced stages of prostate cancer. (See, e.g., [(]Saffran, D., et al., PNAS 10:1073-1078 or the world wide web address [www.]pnas.org/cgi/doi/10.1073/pnas.051624698.)

Please amend the paragraph on page 74, line 30-page 75, line 5, as follows:

Subcutaneous (s.c.) tumors are generated by injection of 1×10^6 LAPC-9, PC3, or PC3-55P4H4 cells mixed at a 1:1 dilution with Matrigel (Collaborative Research) in the right flank of male SCID mice. To test antibody efficacy on tumor formation, i.p. antibody injections are started on the same day as tumor-cell injections. As a control, mice are injected with either purified mouse IgG (ICN) or PBS; or a purified monoclonal antibody that recognizes an irrelevant antigen not expressed in human cells. In preliminary studies, no difference is found between mouse IgG or PBS on tumor growth. Tumor sizes are determined by vernier caliper measurements, and the tumor volume is calculated as length x width x height. Mice with s.c.

tumors greater than 1.5 cm in diameter are sacrificed. PSA levels are determined by using a PSA ELISA kit (Anogen, Mississauga, Ontario). Circulating levels of anti-55P4H4 mAbs are determined by a capture ELISA kit (Bethyl Laboratories, Montgomery, TX). (See, e.g., [(]Saffran, D., et al., PNAS 10:1073-1078 or the world wide web address [www.]pnas.org/cgi/doi/10.1073/pnas.051624698.)

Please amend the paragraph on page 90, lines 14-16, as follows:

Epitopes are often selected that have a binding affinity of an IC50 of 500 nM or less for an HLA class I molecule, or for class II, an IC50 of 1000 nM or less; or HLA Class I peptides with high binding scores form the BIMAS web site at the world wide web address [, http://]bimas.dcrt.nih.gov/.

In the Claims:

66. (Amended) An isolated 55P4H4-related protein that comprises an amino acid sequence [which is exactly that of an amino acid sequence] encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide consisting of the sequence as shown in SEQ ID NO: 1[, wherein T can also be U];

(b) a polynucleotide consisting of the sequence as shown in SEQ ID NO: 1, from nucleotide residue number 204 through nucleotide residue number 782[, wherein T can also be U];

(c) a polynucleotide that [encodes a 55P4H4-related protein whose sequence] is [encoded by] the cDNA[s] contained in the plasmid designated p55P4H4-EBB12 deposited with American Type Culture Collection as Accession No. PTA-1894;

(d) a polynucleotide that encodes a 55P4H4-related protein that is at least 90% homologous to the entire amino acid sequence shown in SEQ ID NO: 2 and which is specifically bound by an antibody that specifically binds the protein of SEQ. ID. No.: 2; and

(e) a polynucleotide that encodes a [55P4H4-related protein that is more than 90% homologous to the entire amino acid sequence shown in] fragment containing at least 30

contiguous amino acids of SEQ ID NO: 2 and which is specifically bound by an antibody that specifically binds the protein of SEQ. ID. No.: 2[;

(f) a polynucleotide that encodes a 55P4H4-related protein that is at least 90% identical to the entire amino acid sequence shown in SEQ ID NO: 2;

(g) a polynucleotide that encodes a 55P4H4-related protein that is more than 90% identical to the entire amino acid sequence shown in SEQ ID NO: 2;

(h) a polynucleotide that is fully complementary to a polynucleotide of any one of (a)-(g); and,

(i) a polynucleotide that selectively hybridizes under stringent conditions to a polynucleotide of (a)-(h)].